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Short communication

Aortic dissection and prophylactic surgery in congenital heart disease

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ABSTRACT

Background: Proximal aortic dilatation in certain congenital heart diseases (CHD) prompts concerns about dissection and consideration of prophylactic surgery. To evaluate contemporary prophylactic practice, we determined incidence of aortic dissection and prophylactic surgery in aortopathy-associated CHD, compared to Marfan syndrom (MFS) and controls.

Methods and results: We followed patients from the CONCOR adult CHD registry (2002–2015), with a native proximal aorta and aortopathy-associated CHD, comprising bicuspid aortic valve/aortic stenosis ('BAV/AS'; n = 2239) and aortic coarctation/conotruncal defects/univentricular heart/ventricular septal defect ('At-risk CHD'; n = 5439). As reference, we selected MFS (n = 356) and 'Control' (atrial septal defect, pulmonary stenosis; n = 2940) patients. Cumulative incidences of dissection and prophylactic proximal aortic replacement – considered competing events – were determined, and compared corrected for age and sex. Median follow-up was 6.7 years. Ten-year dissection-incidence was 0.3% (95%CI: 0.0–0.7) in BAV/AS and 0.2% (0.0–0.3) in At-risk CHD, both significantly lower than in MFS (4.1%; 1.8–6.4) and similar to Controls (0.1%; 0.0–0.3). Ten-year prophylactic-surgery incidence was 9.3% (7.6–11.0) in BAV/AS and 0.7% (0.5–1.0) in At-risk CHD, both significantly lower than in MFS (21.3%; 16.3–26.3) and higher than in Controls (0.1%; 0.0–0.3).

Conclusions: In contemporary practice, aortic-dissection incidence is low in adults with aortopathy-associated CHDs, while prophylactic-surgery incidence is high in BAV/AS. To reduce surgical burden, BAV/AS patients could benefit from more individualised prophylactic-surgery algorithms.

1. Introduction

Proximal aortic dilatation is common in certain congenital heart diseases (CHD), prompting concerns about aortic dissection and consideration of prophylactic aortic replacement [1–3]. Guideline-recommendations for prophylactic surgery are subject to ongoing debate for bicuspid aortic valve (BAV) and lacking for other CHD types [1,4,5]. To evaluate contemporary practice, we determined incidence of aortic dissection (AD) and prophylactic proximal (root/ascending) aortic replacement surgery (PPAR) in patients with aortopathy-associated CHD with a native proximal aorta, compared to Marfan syndrome (MFS) and controls.

2. Methods

2.1. Study population and data collection

The cohort comprised ≥18-year-old patients from the CONCOR Dutch adult CHD registry. The study conforms to the Declaration of Helsinki, and was approved by the ethics boards of all participating centers [6]. Since 2002, after written informed consent, baseline and follow-up clinical events are obtained from medical records. In patients with multiple CHDs, the most severe according to a consensus-based classification is designated the primary CHD [7].

We selected patients with a native proximal aorta (or neo-aorta after arterial switch) at inclusion, and a primary diagnosis of aortopathy-associated CHD, comprising (1) BAV (n = 1815) or aortic stenosis (AS; n = 424) ('BAV/AS'; n = 2239), and (2) 'At-risk CHD' (n = 5439), comprising aortic coarctation (CoA, n = 734), conotruncal defects (n = 2142; tetralogy of Fallot, transposition complex,

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pulmonary atresia, double-outlet right ventricle), univentricular heart (n = 270) and ventricular septal defect (VSD; n = 2293). As reference, we selected patients with MFS (n = 356) and 'Controls' with non-aortopathy-associated CHD (atrial septal defect or pulmonary stenosis; n = 2940). Subjects with BAV and CoA are included as BAV/AS, those with another primary CHD and BAV as a secondary diagnosis were excluded.

Patients were followed for AD and PPAR (not preceded by dissection/rupture; definition: Supplemental Table I). Follow up started 3 months after CONCOR inclusion, to correct for possible inclusion conditional on instantaneous risk (e.g. during (pre)operative hospital admission). Follow-up ended at the outcome, latest medical record review, death or end-of-study (October 10th 2015), whichever occurred first.

Medical/imaging records of 91/130 PPARs in BAV/AS and 24/34 in At-risk CHD patients from high-volume centers were retrospectively reviewed for surgical indications (retrieved: 89 BAV/AS, 24 At-risk CHD) and largest pre-operative aortic diameter (retrieved: 78 BAV/AS, 23 At-risk CHD).

2.2. Statistical analysis

Cumulative incidence function curves were constructed, including AD, PPAR and death as competing events, and compared using Gray's test. Proportional subdistribution hazards regression was performed, correcting for age and sex (additionally correcting for baseline aortic valve replacement [AVR] only marginally affected results) [8]. Additional pairwise analyses were performed. AD fatality, and mortality <3 months after PPAR was assessed and compared between groups. Results from regression analyses are reported as subdistribution hazard ratios (sdHRs) with 95% confidence intervals (CIs) and p-values. Tests were two-sided (alpha: 0.05, Bonferroni correction for multiple comparisons). Analyses were performed using *R* version 3.2.4 (R Foundation, Vienna, Austria) and SPSS version 23 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Baseline characteristics

Baseline characteristics are presented in Table 1. BAV/AS patients were older, and had proportionately more males and baseline AVR than the others. MFS and At-risk CHD were relatively more often followed in tertiary centers.

3.2. Aortic dissection and prophylactic surgery

Table 1 shows the number of incident ADs and PPARs, age at occurrence and mortality. Fig. 1 shows cumulative AD (**A**) and PPAR (**B**) incidence, with results from multivariable regression analyses.

Ten-year cumulative AD incidence was 0.3% (95%CI: 0.0–0.7) in BAV/AS, 0.2%, (0.0–0.3) in At-risk CHD, 4.1% (1.8–6.4) in MFS and 0.1% (0.0–0.3) in Controls (p < 0.001 across groups). Multivariable analyses showed AD risk was significantly higher than in Controls only in MFS (Fig. 1A). Risk was higher in MFS than in both BAV/AS (sdHR = 13.2; 95%CI: 4.2–41.2, p < 0.001) and At-risk CHD (sdHR = 24.2; 9.2–63.8, p < 0.001), and not different in BAV/AS versus At-risk CHD (sdHR = 1.5; 0.4–5.7, p = 0.570). Age at AD was relatively high in Controls, AD fatality relatively low in MFS patients (Table 1, Supplemental Table II).

Ten-year cumulative PPAR incidence was 9.3% (7.6–11.0) in BAV/AS, 0.7% (0.5–1.0) in At-risk CHD, 21.3% (16.3–26.3) in MFS and 0.1% (0.0–0.3) in Controls (p < 0.001 across groups). Multivariable analyses showed significantly higher PPAR incidence compared with Controls in all other groups (Fig. 1B). Risk was higher in MFS than in both BAV/AS (sdHR = 2.6; 1.9–3.6, p < 0.001) and At-risk CHD (sdHR = 30.6; 19.9–47.1, p < 0.001), and higher in BAV/AS than in At-risk CHD (sdHR = 10.2; 6.9–15.1, p < 0.001). Table 1 shows concomitant AVR was more frequent in BAV/AS and At-risk CHD than in MFS. Age at PPAR was similar between groups, and between PPAR with/without AVR (overall and within groups). Three-month PPAR mortality was not significantly different between groups (Table 1).

Supplemental Tables IIIa and IIIb show data concerning indications for PPAR and maximum pre-operative proximal aortic diameters, respectively. All stand-alone PPARs were indicated for aortic dilatation, alone or with aortic insufficiency. For PPAR with AVR, dilatation was the only indication reported in 20% of BAV/AS and 53% of At-risk-CHD cases; the rest included valve dysfunction (p = 0.020). In BAV, mean pre-operative aortic diameter was lower with concomitant AVR (45.1[standard deviation = 7.3]mm, without: 50.0[4.1]mm, p < 0.001),

Table 1
Baseline characteristics and outcome data per group.

	BAV/AS	At-risk CHD	MFS	Control	p-Value[a]
Baseline characteristics					
N	2239	5439	356	2940	
Age, years	35.0 (23.4–48.6)	29.7 (21.6–42.3)	33.8 (24.4–45.6)	39.7 (26.6–54.4)	<0.001[†]
Male	1449 (64.7)	2762 (50.8)	157 (44.1)	1041 (35.4)	<0.001[‡]
AVR	373 (16.7)	93 (1.7)	1 (0.3)	14 (0.5)	<0.001[§]
Tertiary center	1427 (63.7)	3894 (71.6)	320 (89.9)	1641 (55.8)	<0.001[‖]
Follow up time, years					
Median	6.0 (2.8–9.4)	7.1 (3.6–10.3)	9.3 (5.8–11.3)	6.1 (3.0–9.1)	<0.001[¶]
Total	13,959	37,752	2970	17,872	
ADs in follow up					
n	4 (0.2)	6 (0.1)	12 (3.4)	2 (0.1)	
Male	2 (50.0)	4 (66.7)	3 (25.0)	2 (100)	
Age at AD, years	44.3 (34.4–75.1)	48.8 (32.4–69.6)	44.1 (31.2–54.5)	67.7 (64.2-…)	0.506[#]
Fatal AD	3 (75.0)	4 (66.7)	2 (16.7)	2 (100)	0.024[#]
PPARs in follow up					
n	130 (5.8)	34 (0.6)	63 (17.7)	1 (0.0)	
Male	90 (69.2)	25 (73.5)	38 (60.3)	1 (100)	
Concomitant AVR	98 (75.4)	25 (73.5)	19 (30.2)	0 (0.0)	<0.001[**]
Age at PPAR, years	40.7 (29.5–50.4)	37.4 (29.6–47.4)	36.1 (26.6–46.0)	36.2	0.123[#]
Died <3 months after PPAR	2 (1.5)	2 (5.9)	0 (0.0)	0 (0.0)	0.141[#]

Categorical variables are summarized as number (%), and compared using the χ^2 or Fisher's exact test. Continuous variables are summarized as median (interquartile range), and compared using the Kruskal Wallis or Mann-Whitney *U* test.
Abbreviations: AS, aortic stenosis; AVR, aortic valve replacement; BAV, bicuspid aortic valve; CHD, congenital heart disease; MFS, Marfan syndrome.
[a] Overall across-group comparison.
[†] BAV/AS vs MFS: p = NS. All other pairwise: p < 0.008.
[‡] At-risk CHD vs MFS: p = NS. All other pairwise: p < 0.008.
[§] At-risk CHD and Control vs MFS, p = NS. All other pairwise: p < 0.008.
[‖] All pairwise comparisons: p < 0.008.
[¶] BAV/AS vs Control: p = NS. All other pairwise: p < 0.008.
[#] All pairwise: p = NS.
[**] BAV/AS and At-risk CHD vs MFS: p < 0.008. All other pairwise: p = NS.

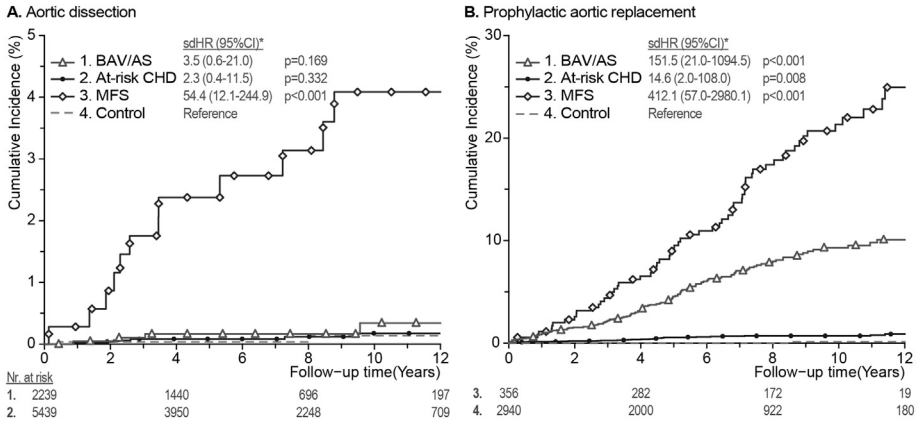

Fig. 1. Cumulative incidence of aortic dissection (A) and prophylactic proximal aortic replacement (B) per group. * Results from multivariable subdistribution hazards regression analysis, including diagnostic group as a categorical variable, correcting for age and sex. Presented as sdHR (95% confidence interval) and p-values. Abbreviations: AS, aortic stenosis; BAV, bicuspid aortic valve; CHD, congenital heart disease; MFS, Marfan syndrome; sdHR, subdistribution hazard ratio.

and if the indication for surgery included valve dysfunction (43.0[6.3] mm, no valve dysfunction: 52.0[3.5]mm, $p < 0.001$). In At-risk CHD, it differed by indication (included valve dysfunction: 44.9[3.2]mm, no valve dysfunction: 54.1[5.6]mm, $p < 0.001$), not by concomitant AVR. In BAV/AS, mean diameter was similar between periods of different guideline-recommended diameter-thresholds for PPAR, and there was no correlation between calendar-time and pre-operative diameters (overall, and stratified by AVR and indication).

Aortic-dissection incidence was not different between patients with BAV with and without CoA, PPAR incidence was significantly higher in the latter (Supplemental Fig. I).

4. Discussion

This study reassuringly shows low aortic-dissection risk in patients with aortopathy-associated CHD types and a native proximal aorta in contemporary practice: similar to controls and much lower than in MFS. Incidence of prophylactic aortic replacement was high in BAV/AS, but not in other aortopathy-associated CHD.

Low aortic-dissection risk in BAV/AS agrees with observations in population-based [1,9] and post-AVR [10] BAV cohorts. The latter also found ~12× lower risk compared to MFS [10]. Present aortic-surgery incidence was comparably high. This is likely due to proportionately more valve dysfunction requiring AVR, a predictor for aortic surgery [9], in our clinical cohort with predominantly native valves. For other aortopathy-associated CHD, low dissection risk in is in line with sporadically reported dissections in these patients, while data on aortic-surgery incidence is lacking [1].

During the study-period (2002–2015), guideline-recommended aortic-diameter thresholds for prophylactic surgery in BAV ranged from conservative (55 mm) in 2002, via aggressive (40 mm) in 2010, back to currently conservative (55 mm, or 50 mm with risk-factors). It ranged between 40 and 50 mm (currently 45 mm) at the time of AVR for dysfunctional BAV [2,3,5]. No specific guidelines for aortic dilatation in other aortopathy-associated CHDs exist [1,2]. While the observational nature of this study precludes conclusions concerning its efficacy, present results reflect clinical practice over the study period.

Regarding BAV/AS, low dissection- and high prophylactic-surgery incidence may either indicate effective contemporary prophylactic practice with justifiably high surgical burden, or substantiate the notion that aggressive guidelines induce unnecessary prophylactic operations, possibly worsening overall outcome [5]. Importantly, many prophylactic aortic replacements were performed with AVR for valve dysfunction, often at moderate dilatation in reviewed cases. However, observational data in BAV patients with moderately dilated aortas showed no long-term difference in dissections or repeat operations compared with isolated AVR [11], while concurrent aortic replacement may increase operative risk [12]. Maximum pre-operative aortic diameters in the present study suggest rather aggressive prophylactic practice, constant over the study-period despite changing guidelines. This may reflect influence of operator and/or patient preference on timing of surgery [4]. Importantly, guidelines are based on nonrandomized data and expert consensus. Moreover, aortic diameter is an imperfect marker for dissection-risk [13], while hemodynamic and genetic factors probably contribute in the heterogeneous BAV-associated aortopathy [4]. Of note, European guidelines consider CoA a risk factor for dissection in BAV patients, eliciting surgery at the reduced (50 mm) threshold [2]. However, we found CoA associated with similar dissection risk, despite lower prophylactic-surgery incidence, in BAV patients. Systematic data and reliable markers for dissection-risk are necessary to provide targeted prophylactic algorithms with a strong evidence-base, and thus improve uniform clinical practice and ultimately reduce surgical burden [4].

Regarding aortopathy-associated CHD other than BAV/AS, dissection-risk was low without frequent surgery. While a restrictive policy following general aortic-disease guidelines (55 mm) seems appropriate in these patients, aortic surgery was sometimes performed at lower aortic diameters, particularly if surgery was indicated for aortic valve dysfunction [1–3].

This study is limited by its observational nature. Known risk-factors for, and determinants of dissection and treatment decisions were unavailable. Locations (proximal/distal) of dissections, important regarding the rationale of prophylactic *proximal* aortic surgery, were not recorded. Surgical indications and pre-operative diameters were retrospectively collected for a proportion of cases. Our clinical cohort from secondary/tertiary centers likely represents a selection with more severe/overt disease from the CHD-population, particularly for BAV, which may remain asymptomatic well into adulthood. Longer follow up in MFS and At-risk CHD reflects CONCOR inclusion starting in tertiary centers, thus including patients with more severe CHD earlier [14].

In conclusion, the present study confirms contemporary aortic risk in aortopathy-associated CHD is much lower than in MFS. As incidence of prophylactic surgery is high in BAV/AS, research should focus on identifying patients at highest risk, to target surgery and reduce surgical burden in BAV/AS patients. A restrictive approach seems appropriate in other aortopathy-associated CHD-types.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.038.

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